REMARKS

Claims 49 and 51-70 were pending in the present application before entry of the present Amendment. Claims 54, 59, and 64 have been canceled without prejudice; Applicants reserve the right to prosecute the subject matter of claims 54, 59, and 64 in one or more related divisional, continuation, and/or continuation-in-part applications. Claims 49, 57, and 58 have been amended to more particularly point out and claim what Applicants consider as the invention. Support for the amendment to claims 49, 57, and 58 can be found in the specification as filed at page 24, lines 3-11 and in section 13, beginning at page 105. Claim 70 has been amended to eliminate the dependency of claim 70 from claim 69, a multiple dependent claim. Instead new claim 71, which depends only from claim 69, has been added. Support for new claim 71 can be found in the specification as filed at page 5, line 31. New claim 72 has been added to more clearly point out and claim what Applicants consider the invention. Support for new claim 72 can be found, *e.g.*, in section 10, beginning at page 63, and section 11, beginning at page 66. Further, new claims 73-83 have been added to more clearly point out and claim what Applicants consider the invention. Support for new claims 73-83 can be found, *e.g.*, in original claim 35. Thus, no new matter has been introduced. Claims 49, 51-53, 55-58, 60-63, 65-83 will be pending upon entry of the present Amendment.

Interview Summary Record

A telephonic interview in connection with the above-identified patent application was held on March 31, 2005 with Supervisory Patent Examiner Mosher Mary, Patent Examiner Zachariah Lucas, Ms. Janet Martineau, Dr. Jacqueline Benn, and Dr. Sebastian Martinek in attendance. Applicants and Applicants' representatives thank Supervisory Patent Examiner Mary Mosher, Patent Examiner Zachariah Lucas for their courtesy during the interview. The Examiner's rejections, specifically the rejections under 35 U.S.C. § 1.112, first paragraph, as set forth in the Office Action of October 6, 2004 were discussed at the Interview.

Dr. Benn briefly described the pending claims in the present application, which are set forth in the List Of Claims above, and started the discussion with the enablement rejection of claims 49-53, which are directed to RSV vaccines. Dr. Benn stated that one of the remaining issues is whether chimpanzees, in which effectiveness of the presently claimed vaccines had been shown, are an art-accepted model and are sufficiently predictive for human use. Dr. Benn pointed out that the art relating to RSV vaccines shows that chimpanzees, which are fully permissive for RSV infections, are in many aspects the best animal model for RSV infections. Examiner Lucas responded that although chimpanzees may be the best animal model for RSV vaccines, this fact is not definitive. Examiner Lucas further stated that the standard is whether the skilled artisan could apply the vaccines that had been proven successful in chimpanzees to humans without undue experimentation. Dr. Benn stated that the applicable standard had been met because data obtained in previous studies in chimpanzees and humans show a correlation between the results in chimpanzees and in humans. Dr. Benn pointed the Examiner's attention to Section 2164.02 of the Manual Of Patent Examining Procedure, which states that "[a] rigorous or an invariable exact correlation is not required." Accordingly, Dr. Benn continued, some fine-tuning to adapt the vaccines that worked in chimpanzees to human use is acceptable. Examiner Lucas responded that no effective RSV vaccine has been used in humans to date. Thus, any data obtained in chimpanzees may not be sufficient because no correlation can be shown with human data. Examiner Lucas added that the breadth of the claims has to be considered as well and that the full breadth of the pending claims is not enabled.

Ms. Martineau asked what else, short of clinical data, could be shown to the Office to prove enablement. Ms. Martineau also pointed out that Investigational New Drug applications ("IND") could be and have been filed with the U.S. Food and Drug Administration ("FDA") based on such animal data and that the Office should not require

more for patentability than the FDA for IND submission. Examiner Lucas responded that the standard applied by the Office is different from the standard of the FDA and that although regulatory approval is not required for patentability, predictability from the data obtained in an animal model to human use may be required. No agreement was reached.

With regard to the enablement rejection of claims 49, and 51-69, which are directed to RSV vaccines and RSV immunogenic compositions, the Examiner stated that the claims are too broad in view of the specification; in particular, the Examiner stated that in view of the high number of possible mutations, the specification does not provide sufficient guidance which of the mutations would result in viruses suitable for vaccine or immunogenic composition formulations and that therefore undue experimentation would be required. Dr. Benn replied that, as set forth in previous responses, the specification provides ample guidance for the claimed vaccine and immunogenic composition formulations: the specification does not only provide numerous assays for determining whether a recombinant virus is suitable for vaccine and immunogenic composition formulations, but the specification also provides a high number of working examples for several different viral genes. Thus, the skilled artisan could determine without undue experimentation which recombinant virus is suitable for vaccine and immunogenic composition formulations. The Examiner responded that the performance of an assay would be too much experimentation because the skilled artisan could not predict in advance whether or not a specific virus is suitable for vaccine and/or immunogenic composition formulations. Supervisory Patent Examiner Mosher and Dr. Benn agreed that this is not the proper standard and that predictability is only one factor to be considered.

THE OBJECTION TO CLAIM 70 SHOULD BE WITHDRAWN

Multiple dependent claim 70 has been objected to because it depends from another multiple dependent claim, claim 69. In response, the dependency of claim 70 from claim 69 has been deleted, and instead, claim 71 has been added. Thus, Applicants respectfully request that the objection to claim 70 be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITH DRAWN

Claims 49-53 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to provide enablement for anti-RSV vaccine compositions. In view of the breadth of the claims and the lack of predictability in the art, the Examiner

contends, the pending claims lack enabling support in the specification. In particular, the Examiner supports the notion of lacking predictability in the art with the assertion that there is presently no art-accepted animal model that is predictive of human responses to RSV vaccines. Applicants respectfully disagree because chimpanzees, which are fully permissive for RSV infection have been accepted as an animal model for RSV infections in humans.

Claims 49, and 51-69 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to provide sufficient enabling support for the claimed vaccines and immunogenic compositions. In particular, it is alleged that Applicants have provided only little guidance for which genetic alterations or modification would result in attenuation of the respiratory syncytial virus. Applicants respectfully disagree because (a) any experimentation required to identify attenuated viral mutants is merely routine; and (b) Applicants provide a large number of working examples of attenuated viruses, strategies for obtaining attenuated viruses, and assays for identifying suitable mutants. Applicants not only provide a large number of substitution, insertion, and deletion mutations that result in attenuation of the virus, Applicants also provide different strategies for generating and evaluating attenuated viruses. These different strategies are also exemplified by working examples.

THE LEGAL STANDARD FOR ENABLEMENT

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

The law also does not require the scope of enablement provided by the specification to mirror precisely the scope of protection sought by the claims. *See In re Fisher*, 166

U.S.P.Q. 18, 24 (C.C.P.A. 1970); *see also In re Wright*, 27 U.S.P.Q.2d 1510 (Fed. Cir. 1993). To be enabled, all the law requires is that the scope of enablement provided by the specification bear a "reasonable correlation" to the scope of the claims. *Id.* Thus, to support a non-enablement rejection, the Examiner must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate the teaching in the specification across the entire scope of the claims. *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995).

In addition, the Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of non-enablement. *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971); MPEP § 2164.02. A patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless there is reason to doubt the objective truth of the teachings which must be relied on for enabling support. *Id.*

Under Section 112, it is not fatal that a certain amount of experimentation may be required to adapt the invention to a specific purpose, provided the experimentation is routine. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). Moreover, considerable amount of experimentation is permitted if it is merely routine or the specification provides a reasonable amount of guidance and direction to perform such experimentation. *In re Jackson*, 217 U.S.P.Q. 804, 807 (PTO Bd. Pt. App. Int. 1982).

CLAIMS 49-53 ARE ENABLED BY THE INSTANT SPECIFICATION

One aspect of the rejection is the alleged lack of predictability in the art. In particular, the Examiner contends that the lack of an art accepted animal model evinces insufficient predictability in the art of RSV vaccines.

In response, Applicants respectfully invite the Examiner's attention to section 2164.02 of the MPEP:

> "[...] if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. . . . . A rigorous or an invariable exact correlation is not required . . ." (emphasis added)

A correlation between data obtained in chimpanzees and in humans has been shown. For example, Wright et al., 1982, Infection and Immunity 37(1):397-400 (cited by the Examiner in the Office Action dated October 6, 2004) describe the attenuated phenotype of RSV *ts*-2 in humans. RSV *ts*-2 had previously been shown to be attenuated in animal model

systems, such as chimpanzees (see Abstract, lines 6-8). Thus, there is clearly a correlation between the virulence of RSV in chimpanzees and the virulence of RSV in humans. Although some fine-tuning may be necessary to obtain a vaccine optimal for human use, Applicants assert that such fine-tuning would not constitute undue experimentation because an animal model to assess the degree of attenuation of the virus does exist. In view of the existing correlation between the degree of attenuation in chimpanzees and the degree of attenuation in humans, Applicants assert that it cannot be said that there is a lack of predictability in the art of RSV vaccines. Combining the existing predictability in the art with the guidance provided in the present specification, the skilled artisan would be fully enabled to make and use the claimed vaccines.

In the Amendment dated July 20, 2004, Applicants had cited Dudas *et al.*, 1998, Clinical Microbiology Reviews 11:430-439 to support the notion that chimpanzees are an art accepted model for RSV infections. The Examiner contends that Dudas only shows that chimpanzees are an experimental model that provides relevant information for a particular immunological situation. The Examiner further contends that attenuation of specific RSV mutants can determined definitely only in human studies. In response, Applicants would like to point out that the relevant information that is obtained in chimpanzees allows one to make predictions as to the effect of certain recombinant RSV mutants in humans. Of course, clinical data will ultimately be required for regulatory approval; however, as discussed above "[a] rigorous or an invariable exact correlation is not required." M.P.E.P. Section 2164.02. Thus, the data presented in Dudas show that the chimpanzee model is sufficiently predictive to allow the skilled artisan to make and use the claimed vaccines without undue experimentation.

Further, with regard to the concern of the Examiner that chimpanzees were mentioned in Dudas as model systems in a specific situation, *i.e.*, young infants who have maternally derived RSV antibody (page 434, left column, second full paragraph), Applicants point out that this is an illustrative use of the chimpanzee model system and there is nothing in Dudas to indicate that chimpanzees are limited to this situation as model system. To re-create the situation in young infants who have maternally derived RSV antibody, chimpanzees had been administered with RSVIG. Applicants assert that this use of the chimpanzee model shows its versatility and not any limitation.

The Examiner also points to Teng et al., 2000, Journal of Virology 74(19): 9317-9321 ("Teng") to support the notion that results in chimpanzees cannot be directly translated into

human results. Applicants respectfully assert that Teng supports the notion that results in chimpanzees are predictive of results in humans. For example, at page 9320, left column, first full paragraph, Teng lists several mutant RSVs in the order of their respective attenuation. Based on this list, Teng deduces which mutant RSV is most likely to be suitable for use in humans. Although Teng continues to say that ultimately clinical trials are necessary, Teng clearly stands for the proposition that chimpanzees do have predictive value as animal model systems for RSV infections in humans.

The Examiner cites Prince et al., 2000, Journal of Virology, 74(22): 10287-10292 ("Prince") for the proposition that the art recognized no anti-RSV vaccines, replicating or non-replicating. Prince briefly summarizes the problems associated with RSV vaccines (first paragraph at page 10287). These problems, however, have been overcome by the present invention as demonstrated by the successful application of the vaccines of the present invention in chimpanzees.

The Examiner further contends that the present application fails to address the problems associated with replicating RSV vaccines and that a large amount of experimentation would be required to develop the claimed vaccines. In particular, the Examiner contends that the art indicates that it would not be immediately obvious to those in the art as to which embodiments would or would not be effective anti-RSV vaccines. Applicants assert that the present invention provides a technology that allows the development of RSV vaccines without undue experimentation. A considerable amount of experimentation is permitted if it is merely routine or the specification provides a reasonable amount of guidance and direction to the experimentation. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988); *In re Jackson*, 217 U.S.P.Q. 804, 807 (PTO Bd. Pt. App. Int. 1982). In the present situation, Applicants provide a technology to introduce mutations into the genome of an RSV and assays for determining whether such mutations will result in attenuation of the virus. Any experimentation that would be involved in the development of the suitable vaccines is merely routine in the art. As discussed in more detail below in connection with the rejection of claims 49 and 51-69, the specification as filed teaches how to introduce mutations, such as insertions, deletions and substitutions of open reading frames, into the viral genome and how to assess whether the modification results in attenuation of the virus and whether the virus is suitable as a vaccine. Thus, the skilled artisan would know how to generate the claimed vaccines without undue experimentation. However, the specification does not stop at teaching how to generate mutant viruses and how to select the

viruses suitable for vaccine formulations, the application as filed also describes strategies for mutating viruses that will yield the viruses suitable for vaccine formulation. Further, the specification as filed discloses an abundance of different mutant viruses that were actually generated, thereby providing guidelines for the skilled artisan of how to generate viruses suitable for vaccine formulations.

CLAIMS 49 AND 51-69 ARE ENABLED BY THE INSTANT SPECIFICATION

The gravamen of the Examiner's rejection of claim 49 and 51-69 is that the art of isolating and characterizing new attenuated viruses is unpredictable and that any experimentation that is required to isolate and characterize the claimed proteins is undue in view of the present specification.

The invention relates to a composition comprising RSV with certain genetic modifications. The invention provided for the first time the possibility to genetically engineer the viral genome of a non-segmented negative-stranded RNA viruses, such as RSV, to include such modifications.

The specification as filed teaches how to introduce mutations, such as insertions, deletions and substitutions of open reading frames, into the viral genome and how to evaluate the effect of the mutation on the viability of the mutated virus. Thus, the skilled artisan would know how to generate the claimed viruses without undue experimentation. However, the specification does not stop at teaching how to generate mutant viruses and how to select the claimed viruses, the application as filed also describes strategies for mutating viruses that will yield the claimed viruses. Further, the specification as filed discloses an abundance of different mutant viruses that were actually generated, thereby providing guidelines for the skilled artisan of how to generate the claimed viruses.

Applicants respectfully point out that enabling support for the claimed compositions is provided throughout the specification in form of guidance on how viruses with an attenuated phenotype can be generated. The specification provides numerous examples of deletions, insertions, and substitutions in the genome of RSV that result in an attenuated phenotype. For example, in section 8, beginning at page 50, it is shown that a mutation in the leader sequence (rRSV4G) can result in attenuation. Further, it is shown that insertion of the G gene of subgroup B of RSV in the genome of recombinant RSV of subgroup A (rRSVA2(B-G)) also results in attenuation.

The generation of attenuating L gene mutants is described in section 9, beginning at page 57. The CAT minigenome assay, a preliminary assay for identifying suitable mutations and thus to facilitate the identification of attenuated viral mutants, is described on page 59, lines 9-18. Briefly, the functionality of L gene mutants can be tested using the CAT minigenome assay. The skilled artisan would know that this system can be used to exclude mutants that would result in lethality of the virus caused by inactivity of the L gene and to exclude mutants that would not result in attenuation because the mutant L gene product is as active as the wild type L gene product. A strategy for obtaining temperature-sensitive L gene mutations is discussed at page 57, lines 14-22. Examples of L gene mutations and their effect in the CAT minigenome assay are set forth in Table 2 at page 61.

Section 10, beginning at page 63, describes the generation of infectious virus with M2-2 deletion, SH deletion, and SH/M2-2 deletion. Section 11, beginning at page 66, discusses the generation and attenuating effects of M2-2 deletion, SH deletion, NS1 deletion, NS2 deletion, M2-2/SH deletion, M2-2/NS1 deletion, NS2/M2-2 deletion, NS1/NS2 deletion, NS1/SH deletion, NS2/SH deletion, and NS1/NS2/SH deletion. Most of these deletion mutants were not only recovered as infectious viruses but were also shown to be attenuated. Mutagenesis of the M2-1 gene is described in section 12, beginning at page 100. Attenuated mutants were recovered as shown in Table 19, page 103. Furthermore, the importance of the Zn-binding motif in M2-1 is discussed at page 103, lines 1-5, thus providing guidance for the skilled artisan, *i.e.*, to maintain the integrity of the Zn-binding motif. The C-terminal truncations of M2-1 that are described in section 12.2, beginning at page 103, provide the skilled artisan with the information of how far M2-1 can be truncated without being lethal to the virus. Substitutions of the G and F gene are described in section 13, beginning at page 105, and also result in attenuation.

In sum, the Application not only provides specific examples of substitutions, insertions, and deletions that result in attenuation of the virus, Applicants also provide strategy and guidance for obtaining additional attenuating mutants as well as an assay suitable to routinely screen for attenuated mutants. In particular, Applicants identify many different targets for attenuating mutations in the RSV genome. Thus, the instant specification, together with information which was readily available to the skilled artisan at the time the instant application was filed, provides a disclosure which fully enables the claimed viruses.

The Examiner also contends that mutations in the RSV genome would achieve varied results and that the art is therefore unpredictable. Applicants respectfully respond, that, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, ... then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act. *Id.* at 219.

Applicants would like to direct the Examiner's attention to the situation in *Angstadt*. In *Angstadt*, the Applicants had developed a catalytic process using organometallic complexes. The board rejected the claims because the specification did not "give any information as to how the operative catalysts might be determined without undue experimentation." *Id.* at 216. The court, in rejecting the board's decision concluded that the skilled artisan armed with the specification and its 40 working examples would have been easily able to "determine which of the catalyst complexes within the scope of the claims work." *Id.* at 218. The court also held that the determination of which catalysts work does not "require ingenuity beyond that to be expected of one of ordinary skill in the art." *Id.* The *Angstadt* court further states that "the performance of trial runs using different catalysts is 'reasonable,' even if the end result is uncertain." *Id.* at 219 (emphasis added).

Angstadt further states:

> What the dissent seems to be obsessed with is the thought of catalysts which *won't* work to produce the intended result. Appellants have *enabled* those in the art to see that this is a real possibility, which is commendable frankness in a disclosure. Without undue experimentation or effort or expense the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do not cover them. The dissent wants appellants to make everything predictable in advance, which is impracticable and unreasonable.

Similarly, in the present application, simply because certain mutations in the genome of RSV will result in lethality of the virus, does not mean that the claimed invention is not enabled. As discussed above, the specification teaches how mutant viruses can be generated and how the attenuated viruses can be identified. The specification also discloses an abundance of specific mutations that were made and analyzed to provide guidance to the skilled artisan for generating the claimed viruses.

The Examiner points to Bowie (Science 247:1306-1310; "Bowie") to support the position that the art of protein modification is unpredictable. As discussed above in the context of *Angstadt*, a claimed invention is enabled even if the outcome of a particular embodiment is uncertain, as long as the testing involved is "reasonable." Testing whether a particular mutant virus is attenuated is certainly well within the ability of the skilled artisan and does not involve any unreasonable experimentation.

Accordingly, Applicants respectfully request that the rejection of claims 49, and 51-69 under 35 U.S.C. 112, first paragraph, be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 102(b) SHOULD BE WITH DRAWN

Claims 49, 52, 54, 57, 58, 59, 63, 64, and 68 are rejected as allegedly being anticipated by Wright et al, 1982, Infection and Immunity, 37(1):397-500 ("Wright I"). Further, claims 49, 51, 52, 54, 57, 58, 59, 62, 63, 64, 67, and 68 are rejected as allegedly being anticipated by Wright et al, 1977, Journal of Pediatrics 88(6):931-936 ("Wright II"). Without making any admission with regard to the merits of the rejection and solely to expedite the prosecution of the present application, Applicants respectfully assert that in view of the present amendment the rejections over Wright I and Wright II should be withdrawn.

Neither Wright I nor Wright II uses RS viruses in which deletions, insertions, or substitutions of an entire open reading frame have been introduced into the genome of the virus. Rather, the RS mutants used in Wright I are the result of single point mutations introduced by exposure of the virus to chemical mutagens. The rejected claims have been amended to recite that the genetic modification is (i) a deletion, (ii) an insertion, or (iii) a substitution of an entire open reading frame.

THE LEGAL STANDARD FOR ANTICIPATION

The standard for an anticipatory reference is set forth in *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987): "[a] claim is anticipated only if each

and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See also Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989)(holding that "[t]he identical invention must be shown in as complete detail as is contained in the . . . claim"). Further, a prior art reference must be an *enabling* reference to anticipate. See *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986) ("the prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public."). *See also* MPEP § 2121.01; *In re Hoeksema*, 399 F.2d 269 (C.C.P.A. 1968) ("In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'.").

NEITHER WRIGHT I NOR WRIGHT II ANTICIPATES THE PRESENT INVENTION

Wright I describes the administration RSV mutant *ts*-2 to adults and children. Wright II describes the administration RSV mutant *ts*-1 to infants as live attenuated experimental vaccine. The *ts*-2 and *ts*-1mutants were generated by exposure of the RSV to mutagens, such as 5-FU and NTG, to result in point mutations in the genome of RSV (Gharpure et al., 1969, J Virol 3(4):414-421; "Gharpure"). Gharpure determines that the frequency of resulting temperature sensitive mutants, such as *ts*-2 and *ts*-1, and the low concentration of mutagens used is consistent with the generation of single nucleotide mutants (Gharpure at p. 419, col. 1). The stability of the mutants generated as determined by the reversion rate indicates that the temperature sensitive phenotype is the result of one or more point mutations introduced into the viral genome. Neither Wright I nor Wright II teaches or suggests that mutations other than single point mutations, such as insertions or deletions, can be introduced into the genome of the virus. Because neither Wright I nor Wright II teaches all the elements of the claimed invention, it cannot anticipate the claimed invention. Hence, the rejections over Wright I and Wright II should be withdrawn.

CROWE DOES NOT ANTICIPATE THE PRESENT INVENTION

Claims 49, 51, 52, 54, 57, 58, 59, 62, 63, 64, 67, and 68 are rejected as allegedly being anticipated by Crowe et al., 1993, Vaccine 11(14):1395-1404 ("Crowe"). Without making any admission with regard to the merits of the rejection and solely to expedite the

prosecution of the present application, Applicants respectfully assert that in view of the present amendment, the rejection over Crowe should be withdrawn.

The legal standard for an anticipatory reference is set forth above.

Crowe describes the administration RSV mutants *ts*-1, *ts*-1-*NG1*, and *ts*-4 to chimpanzees as live attenuated experimental vaccine. The temperature-sensitive mutants were generated by exposure of the RSV to mutagens, such as 5-FU and NTG, to result in point mutations in the genome of RSV (see Crowe at page 1396, right column, section "Viruses"). Crowe does not teach nor suggest that mutations other than single point mutations, such as insertions or deletions, can be introduced into the genome of the virus. Because Crowe does not teach all the elements of the claimed invention, it cannot anticipate the claimed invention. Hence, the rejection over Crowe should be withdrawn.

Applicants respectfully request that the rejections under 35 U.S.C. § 102(b) of claims 49 to 53 should be withdrawn.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing amendments and remarks. No new matter has been introduced. The claims are believed to be free of the art and patentable. Withdrawal of all the rejections and an allowance are earnestly sought.

Respectfully submitted,

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